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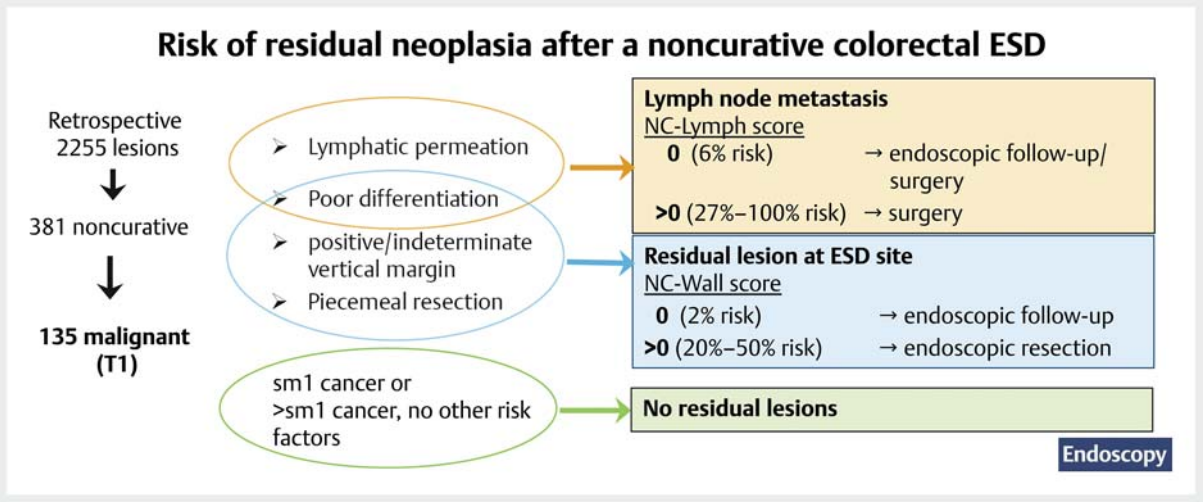
Risk of residual neoplasia after a noncurative colorectal endoscopic submucosal dissection for malignant lesions: a multinational study

GRAPHICAL ABSTRACT



Authors

João Santos-Antunes[1,2], Mathieu Pioche[3], Felipe Ramos-Zabala[4], Paolo Cecinato[5], Francisco J. Gallego Rojo[6], Pedro Barreiro[7,8], Catarina Félix[7], Sandro Sferrazza[9], Frieder Berr[10], Andrej Wagner[10], Arnaud Lemmers[11], Mariana Figueiredo Ferreira[11], Eduardo Albéniz[12], Hugo Uchima[13,14], Ricardo Küttner-Magalhães[15], Carlos Fernandes[16], Rui Morais[1], Sunil Gupta[17], Daniel Martinho-Dias[18], Elisabete Rios[19], Isabel Faria-Ramos[2], Margarida Marques[1], Michael J. Bourke[17], Guilherme Macedo[1]

Institutions

1 Gastroenterology Department, Faculty of Medicine, Centro Hospitalar Universitário S. João, Porto, Portugal
2 Ipatimup/i3S (Instituto de Investigação e Inovação em Saúde da Universidade do Porto), Porto, Portugal
3 Department of Hepatology and Gastroenterology, Edouard Herriot Hospital, Lyon, France
4 Department of Gastroenterology, Department of Clinical Medical Sciences, Hospital Universitario HM Montepríncipe, HM Hospitales, Universidad San Pablo-CEU, CEU Universities Madrid, Madrid, Spain
5 Gastroenterology and Digestive Endoscopy Unit, Azienda USL – IRCCS di Reggio Emilia, Reggio Emilia, Italy
6 Gastroenterology Department, Hospital de Poniente, Almería, Spain
7 Gastroenterology Department, Centro Hospitalar Lisboa Ocidental EPE, Lisbon, Portugal
8 Lisbon Advanced Endoscopic Center, Hospital Lusíadas, Lisbon, Portugal
9 Gastroenterology and Endoscopy Unit, Santa Chiara Hospital, Trento, Italy
10 Department of Internal Medicine I, University Clinics Salzburg, Paracelsus Medical University, Salzburg, Austria
11 Department of Gastroenterology, Hepatopancreatology and Digestive Oncology, CUB Erasme Hospital, Université Libre de Bruxelles (ULB), Brussels, Belgium
12 Navarrabiomed Research Institute, Complejo Hospitalario de Navarra, Public University of Navarra, IdiSNA, Pamplona, Spain
13 Digestive Endoscopy Service, Centro Médico Teknon, Barcelona, Spain
14 Gastroenterology Service, Hospital Universitario Germans Trias i Pujol, Barcelona, Spain
15 Gastroenterology Department, Hospital Santo António, Centro Hospitalar Universitário do Porto, Porto, Portugal
16 Gastroenterology Department, Centro Hospitalar de Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal
17 Department of Gastroenterology and Hepatology, Westmead Hospital, Sydney, Australia

18 Department of Community Medicine, Information and Decision in Health, Faculty of Medicine, University of Porto, Porto, Portugal
19 Pathology Department, Faculty of Medicine, Centro Hospitalar Universitário S. João, Porto, Portugal

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Fig. 1 s, Tables 1 s–2 s
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Corresponding author
João Santos-Antunes, MD, Gastroenterology Department, Centro Hospitalar S. João, Al. Prof. Hernani Monteiro, 4200-319, Porto, Portugal
joao.claudio.antunes@gmail.com

ABSTRACT

Background Endoscopic submucosal dissection (ESD) in colorectal lesions is technically demanding and a significant rate of noncurative procedures is expected. We aimed to assess the rate of residual lesions after a noncurative ESD for colorectal cancer (CRC) and to establish predictive scores to be applied in the clinical setting.

Methods Retrospective multicenter analysis of consecutive colorectal ESDs. Patients with noncurative ESDs performed for the treatment of CRC lesions submitted to complementary surgery or with at least one follow-up endoscopy were included.

Results From 2255 colorectal ESDs, 381 (17 %) were noncurative, and 135 of these were performed in CRC lesions. A residual lesion was observed in 24 patients (18 %). Surgery was performed in 96 patients and 76 (79 %) had no residual lesion in the colorectal wall or in the lymph nodes. The residual lesion rate for sm1 cancers was 0 %, and for > sm1 cancers was also 0 % if no other risk factors were present. Independent risk factors for lymph node metastasis were poor differentiation and lymphatic permeation (NC-Lymph score). Risk factors for the presence of a residual lesion in the wall were piecemeal resection, poor differentiation, and positive/indeterminate vertical margin (NC-Wall score).

Conclusions Lymphatic permeation or poor differentiation warrant surgery owing to their high risk of lymph node metastasis, mainly in > sm1 cancers. In the remaining cases, en bloc and R0 resections resulted in a low risk of residual lesions in the wall. Our scores can be a useful tool for the management of patients who undergo noncurative colorectal ESDs.

Introduction

Endoscopic submucosal dissection (ESD) allows an en bloc resection irrespective of the size and morphology of the lesion. This is essential for a precise pathological evaluation and for its lower risk of recurrence compared with piecemeal resection by endoscopic mucosal resection (EMR) [1]. In the last decades, ESD has been applied with very good outcomes, not only in stomach but also in the esophagus, colon, and rectum [2–4]. Even though the majority of colorectal lesions can still be managed by EMR [5], the role of ESD in this context has been growing in the West [6, 7], particularly in lesions with a higher risk of harboring malignancy, such as nongranular laterally spreading tumors (LSTs) [8] and large granular mixed-type LSTs [9, 10], as well as all those that present with other high risk features on endoscopic evaluation [8]. Nevertheless, ESD is technically challenging, with a long learning curve [11]. Depending on the experience of the endoscopist and lesion characteristics, it is expected that a significant number of ESDs will not complete all the requisites for being considered curative [12].

The European Society of Gastrointestinal Endoscopy (ESGE) renamed curative resection as “low risk resection”, and redefined noncurative ESD (NC-ESD) as “local risk resection” (LocRR) or “high risk resection” (HRR), depending on the presence of classic low or high risk features, respectively [13]. For LocRR procedures, endoscopic follow-up may be sufficient; in HRR, complementary treatment is usually warranted owing to the risk of lymph node metastasis (LNM). Nonetheless, the best strategy for NC-ESDs is still under debate, as the different criteria for HRR may not carry the same independent risk for LNM or residual lesions. This is of critical importance because an inaccurate selection of patients may lead to a significant proportion of unnecessary surgical procedures, with consequent morbimortality.

The aim of this multicenter project was to evaluate all of the consecutive NC-ESDs performed in several Western reference centers, assessing the rate of residual lesions in the surgical specimen or during endoscopic follow-up in malignant lesions, in order to search for predictors of local residual disease or locoregional LNM.

Methods

Study design and patient selection

We performed a retrospective multicenter analysis of prospectively collected registries of consecutive patients undergoing colorectal ESD between November 2009 and June 2021. A total of 15 centers in Portugal, Spain, France, Belgium, Italy, Austria, and Australia agreed to participate. All of the endoscopists had performed at least 100 ESDs at the time of data collection; however, in some cases, this series included all of the procedures that were performed since the beginning of ESD practice in a center, so were early on the learning curve. The development of this endoscopic technique at each center allowed all of the specimens to be analyzed by expert gastrointestinal pathologists. Although the histological report could not be standardized owing to the retrospective design of the study, a systematic approach was followed in each center to document an accurate histopathological diagnosis, agreed upon by pathologists and expert interventional endoscopists, according to international standards. Missing data from the initial database led to direct contact with study centers to provide further details if available.

The indication for ESD was the presence of a colorectal neoplastic lesion without endoscopic features of deep invasive (> sm1) adenocarcinoma [13, 14]. Only patients with an NC-ESD (LocRR or HRR) done for colorectal cancer (at least T1 cancer) who underwent surgery or had at least one follow-up endoscopy were selected for further analysis.

The Ethics Board approved the study (reference number 255/2020).

Definitions and outcomes

An en bloc resection was recorded if the target lesion had been retrieved in a single specimen, or piecemeal resection if it was removed in more than one fragment. An R0 resection was recorded when pathological evaluation showed free horizontal and vertical margins in an en bloc resected specimen.

Colorectal curative resections were R0 lesions, with low or high grade dysplasia, or well to moderately differentiated mucosal or superficial submucosal (sm1; < 1000-µm vertical submucosal invasion) adenocarcinoma, without lymphovascular invasion. All other resections were considered NC-ESDs, as well as those that presented with tumor budding [15].

Metachronous neoplasia in locations other than the ESD site, local recurrence or metastatic disease in the long-term, and differences between curative and NC-ESDs were not assessed (outside the scope of this study).

The major outcome parameters were: the rate of residual dysplastic lesions in the scar after an NC-ESD, observed in the follow-up endoscopies (confirmed by pathological analysis) or in the surgical specimens, as well as the rate of LNM in patients who underwent surgery. Our goal was then to explore the risk factors and weigh these in order to create predictive scores for local residual disease and for locoregional LNM.

Statistical analysis

Categorical variables were described as absolute (n) and relative frequencies (%). Mean and SD, or median and interquartile range (IQR) were used for continuous variables as appropriate. Normal assumptions were verified to ensure correct test selection. Continuous variables were then compared using either the Student's *t* test or Mann–Whitney test, while the chi-squared test or Fisher's exact test were used for categorical variables, as appropriate.

First, univariate bivariable analyses were conducted in order to identify potential predictors for LNM or residual lesions at the ESD site. Those predictors significantly associated with the outcome were then considered for stepwise backward binomial logistic regression, with either LNM or a residual lesion at the ESD site as the dependent variable. A *P* value of < 0.10 was defined as the cutoff for inclusion of the assessed factors in the final risk model.

The relative weights of the predictors (as described by β regression coefficient values, rounded to the nearest integer) were used to create a clinical score. No interactions with statistical significance were verified between the variables within the models. The performance of the score was evaluated using a receiver operating characteristic (ROC) curve. We assessed the calibration of the model with the Hosmer–Lemeshow goodness-of-fit test. The model was validated internally using the resampling validation method for logistic models with 100 bootstrap resamples and the *c* statistic was used to evaluate the discrimination of the models. Bias-corrected and accelerated (BCa) 95 %CIs for the *c* statistic were then calculated.

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) v.25 and R version 4.1.2.

Results

Sample and procedures description

Among 2255 colorectal ESDs, 381 (17 %) were identified as being noncurative. A total of 352 ESDs were performed in epithelial lesions that had available follow-up data, with at least one endoscopy or surgery being performed. Most of the lesions were T1 cancers (n = 135; 38 %), Tis (n = 36; 10 %), or high grade dysplasia (n = 97; 28 %). The remainder were low grade dysplasia (n = 76; 22 %), or serrated (n = 6; 2 %) and anorectal squamous cell cancer lesions (n = 2; 1 %). The two anorectal squamous cell cancers were further excluded from the analysis owing to their rarity and because they represented a separate tumor entity that was not part of the indications for colorectal ESD [13, 14]. Therefore, 135 lesions were at least T1 adenocarcinomas and were included in this ongoing study (▶ **Table 1**; **Fig. 1 s**, see online-only Supplementary material).

The majority of the patients were male (62 %), with a mean (SD) age of 66 (10) years. There were 60 colonic lesions (44 %) and 75 rectal lesions (56 %). The median lesion and specimen

▶ **Table 1** Baseline characteristics of the cohort of 135 patients with at least T1 adenocarcinoma who were included in this study, their lesions, and the procedures they underwent.

Patient characteristics	
Sex, n (%)	
▪ Male	84 (62)
▪ Female	51 (38)
Age, mean (SD), years	66 (10)
Lesion characteristics	
Lesion size, median (IQR), mm	40 (26–60)
Paris classification, n (%)	
▪ Is	31 (23)
▪ IIa	30 (22)
▪ IIa + Is	40 (30)
▪ Any IIc component	29 (21)
▪ Other	5 (4)
Location, n (%)	
▪ Colon	60 (44)
▪ Rectum	75 (56)
Laterally spreading tumor (LST) morphology, n (%)	
▪ Granular homogeneous	13 (10)
▪ Granular nodular mixed-type	53 (39)
▪ Nongranular flat-elevated	12 (9)
▪ Nongranular pseudodepressed	18 (13)
▪ Non-LST morphology	39 (29)
Procedure characteristics	
ESD duration, median (IQR), minutes	100 (60–168)
Complementary techniques	
▪ None	93 (69)
▪ Knife-assisted resection/hybrid	28 (21)
▪ Traction clip-line	2 (1)
▪ Pocket-creation method	10 (7)
▪ Underwater	2 (1)
Resection type	
▪ En bloc	123 (91)
▪ Piecemeal	12 (9)
Histopathological analysis	
Endoscopic submucosal dissection staging	
▪ sm1 adenocarcinoma	15 (11)
▪ >sm1 adenocarcinoma	120 (89)
Differentiation	
▪ Well	45 (33)
▪ Moderate	73 (54)
▪ Poor	17 (13)
Lymphatic permeation	
▪ Positive	17 (13)
▪ Negative	118 (87)
Venous permeation	
▪ Positive	13 (12)
▪ Negative	99 (88)
▪ Not reported	23
Horizontal margin	
▪ Positive/indeterminate	24 (18)
▪ Negative	111 (82)
Vertical margin	
▪ Positive/indeterminate	71 (53)
▪ Negative	64 (47)
Tumor budding	
▪ Positive	51 (39)
▪ Negative	79 (61)
▪ Not reported	5

IQR, interquartile range.

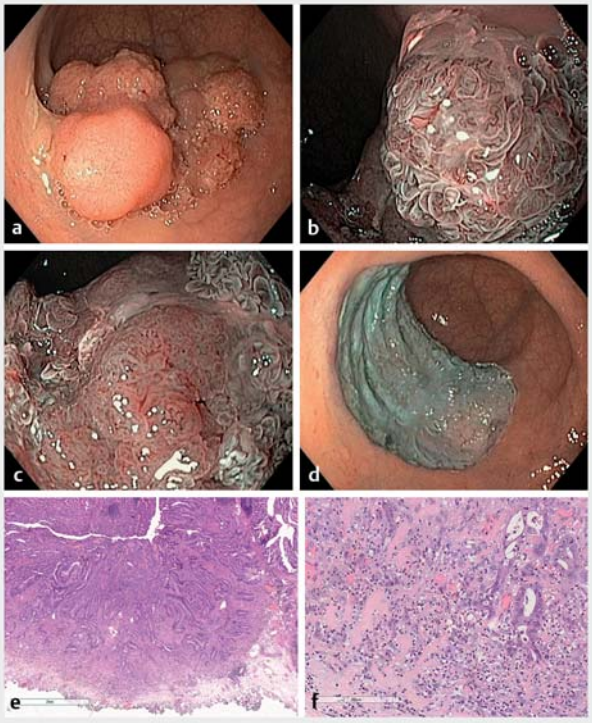
size were 40 mm (IQR 26–60 mm) and 41 mm (IQR 29–66 mm), respectively. The median duration of the ESD procedures was 100 minutes (IQR 60–168 minutes). Most of the cases were performed in granular mixed nodular LSTs (39 %). Three patients (2 %) needed surgery because of ESD adverse events. The ESD mortality rate was 0 %.

Follow-up of patients with noncurative lesions

There were eight patients who refused surgery, and 15 that had criteria for surgery but, after multidisciplinary conference discussions, were only followed-up by endoscopy owing to their age and co-morbidities. From the remaining patients, we report a total of 96 (71 %) patients who underwent surgery for an NC-ESD. Among these, 16 (18 %) developed serious adverse events of surgery and one patient died. From the patients who did not undergo surgery, the median endoscopic follow-up time was 12 months, and this was similar for the patients who presented with or without a residual lesion (11 vs. 12 months, respectively; $P = 0.28$).

Presence of residual lesion after an NC-ESD for colorectal cancer

Among the 135 cancer lesions, 15 (11 %) had sm1 submucosal invasion, with the remainder having deeper invasion. The proportion of patients with >sm1 invasion was similar in the colon and the rectum (93 % and 85 %, respectively; $P = 0.14$).



▶ **Fig. 1** An example case of lymph node metastasis (LNM) following a noncurative endoscopic submucosal dissection (NC-ESD) showing: **a–d** endoscopic images of one of the few cases of LNM (1 positive ganglion out of 12) in a patient with an NC-Lymph score of 0; **e,f** histological images of: **e** submucosal adenocarcinoma; **f** with the presence of tumor budding.

A total of 24 patients (18 %) showed a residual lesion (20 in the surgical specimen and 4 during endoscopic follow-up). No differences were found between centers regarding recurrence, either globally ($P = 0.55$) or when separately analyzing patients who were operated on ($P = 0.30$) and those who were not ($P = 0.97$). Risk factors were poor differentiation ($P < 0.001$), positive/indeterminate vertical resection margin (VM + /VMx; $P = 0.02$), lymphatic permeation ($P = 0.007$), and piecemeal resection ($P = 0.002$).

Overall, the rate of LNM was 14 % and the rate of residual lesions in the wall was 13 %. However, the rates of LNM or a residual lesion in the wall were 0 % after NC-ESD of T1 sm1 cancers. For colorectal cancer with deeper submucosal invasion, 24 % had residual lesions; however, in those lesions without any other risk factors, such as poor differentiation, positive horizontal margins, VM + , lymphatic permeation, or venous invasion, the risk of LNM or lesions in the wall was also 0 %.

Among patients who were not operated on (n = 39), four (10 %) showed a residual benign lesion in the scar that was treated by endoscopic resection. The presence of LNM in this group of patients was not considered for score calculation because we considered only patients with histologically proven LNM (in the surgical specimen). Follow-up imaging was available in 32 of these patients (31 with computed tomography scanning and one with magnetic resonance imaging). Only one patient who did not initially undergo surgery because of co-morbidities presented with metastatic disease and is currently receiving chemotherapy. Overall survival was 90 % in this group after a median follow-up time of 17 months (IQR 10–36 months); deaths reported in this group were unrelated to the lesion that motivated the ESD.

Predictive score for the presence of LNM

Among patients who underwent surgery (n = 96), 20 (21 %) showed a residual lesion in the wall, LNM, or both. An example case of an NC-ESD with LNM is illustrated in ▶ **Fig. 1**.

Risk factors for LNM were poor differentiation ($P = 0.002$), lymphatic permeation ($P < 0.001$), and venous permeation ($P = 0.03$) (▶ **Table 2**). After logistic regression, only poor differentiation and lymphatic permeation remained independently related to LNM and were therefore selected to create a predictive score (NC-Lymph score; β regression coefficient values for poor differentiation, lymphatic permeation, and model intercept of 1.474, 2.028, and −4.775, respectively); lymphatic permeation was scored with 2 points and poor differentiation with 1 point (Hosmer–Lemeshow goodness-of-fit $\chi^2 = 0.190$; $P = 0.91$). Patients scoring 0, 1, 2, or 3 had a 6 %, 25 %, 30 %, and 75 % chance of LNM ($P < 0.001$). Owing to the absence of LNM among sm1 cancers, this score could be applied only in cases with > sm1 invasion, with similar risk rates (**Table 1 s**). Bootstrap resampling showed similar results in the model, with *c* statistic of 0.766 (BCa 95 %CI 0.623–0.903). Example histological images for the different scores are shown in ▶ **Fig. 2**.

After surgery, follow-up was available for 84 patients: 72 with endoscopic follow-up and 79 with radiological follow-up (67 had both). No evidence of endoscopic recurrence was found, but there are two patients with metastatic disease who are receiving treatment. One patient with severe co-morbidities who showed LNM in the surgical specimen died 2 years after the ESD, with radiological signs of disease progression. Another two patients in this group died because of adverse events from surgery. The overall survival rate was 96 % in this group after a median time of 24 months (IQR 13–36 months).

Predictive score for the presence of a residual lesion in the colorectal wall

Among patients with malignant lesions (n = 135), risk factors for the presence of a residual lesion in the wall were piecemeal resection ($P < 0.001$), poor differentiation ($P = 0.03$), and VM + /VMx ($P = 0.002$) (▶ **Table 3**). On multivariate analysis, all of these remained independently associated, with a relative weight of 1 for poor differentiation and 2 for piecemeal resection and VM + /VMx (Hosmer–Lemeshow goodness-of-fit $\chi^2 = 0.860$; $P = 0.84$; β regression coefficient values of 1.773, 1.389, 1.718, and −6.057 for piecemeal resection, poor differentiation, VM + /VMx, and model intercept, respectively). Bootstrap resampling showed similar results in the model, with *c* statistic of 0.792 (BCa 95 %CI 0.680–0.876).

Patients with an NC-Wall score of 0 had a 2 % chance of a residual lesion in the colorectal wall, raising to 100 % in those with an NC-Wall score of 5. Patients were considered low risk with a score of 0 (negative predictive value of 98 %), moderate risk

▶ **Table 2** Risk factors for the presence of lymph node metastasis among the 96 patients who underwent surgery after a noncurative endoscopic submucosal dissection (ESD) performed for the treatment of colorectal cancer.

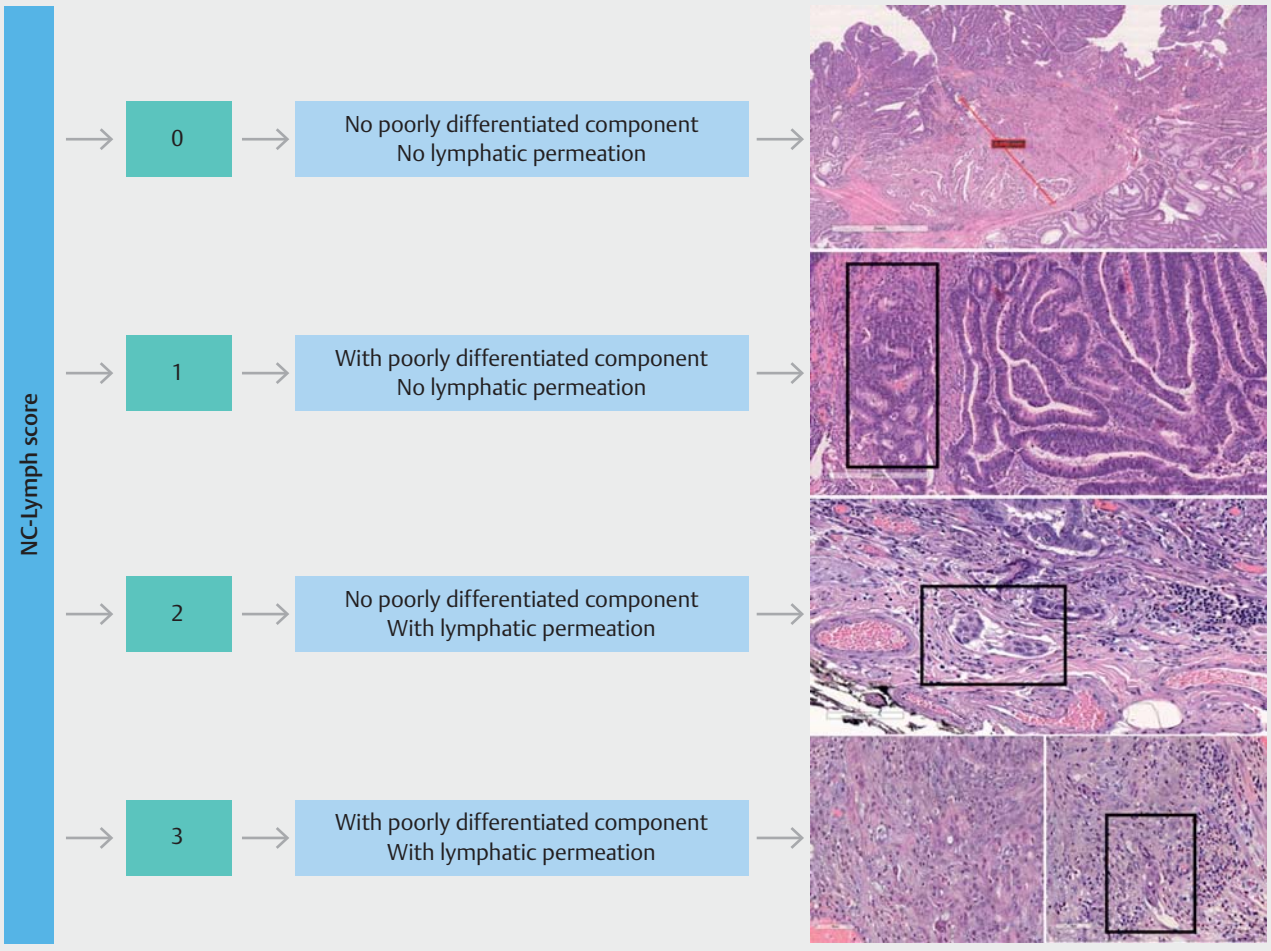
	n	Lymph node metastasis		*P* value
		Yes	No	
Patient characteristics				
Sex, n (%)				0.44
▪ Male	57	9 (16)	48 (84)	
▪ Female	39	4 (10)	35 (90)	
Age, mean (SD), years	96	65 (10)	65 (10)	0.97
Lesion characteristics				
Lesion size, median (IQR), mm	96	50 (29–60)	40 (25–50)	0.25
Paris classification				0.90
▪ Is	25	4 (16)	21 (84)	
▪ IIa	20	3 (15)	17 (85)	
▪ IIa + Is	27	5 (19)	22 (81)	
▪ Any IIc component	21	2 (10)	19 (90)	
▪ Other	3	0	3 (100)	
Location				0.85
▪ Colon	54	7 (13)	47 (87)	
▪ Rectum	42	6 (14)	36 (86)	
Laterally spreading tumor morphology				0.65
▪ Granular homogeneous	9	0	9 (100)	
▪ Granular nodular mixed-type	36	6 (17)	30 (83)	
▪ Nongranular flat-elevated	9	1 (11)	8 (89)	
▪ Nongranular pseudodepressed	13	1 (8)	12 (92)	
Procedure characteristics				
ESD duration, median (IQR), minutes	96	120 (90–185)	100 (60–159)	0.21
Complementary techniques				0.50
▪ Knife-assisted resection/hybrid	24	2 (8)	22 (92)	
▪ Traction clip-line	2	0	2 (100)	
▪ Pocket	7	0	7 (100)	
▪ Underwater	2	0	2 (100)	
▪ None	61	11 (18)	50 (82)	
Resection type				0.07
▪ En bloc	88	10 (11)	78 (89)	
▪ Piecemeal	8	3 (38)	5 (62)	
Histopathological analysis				
ESD staging				0.35
▪ sm1	11	0	11 (100)	
▪ >sm1	85	13 (15)	72 (85)	
Differentiation				**0.002**
▪ Well/moderate	80	7 (6)	73 (94)	
▪ Poor	16	6 (38)	10 (62)	
Lymphatic permeation				**<0.001**
▪ Present	14	6 (43)	8 (57)	
▪ Absent	82	7 (8)	75 (92)	
Venous permeation				**0.03**
▪ Present	10	4 (40)	6 (60)	
▪ Absent	86	9 (11)	77 (89)	
Horizontal margin				0.38
▪ Positive/indeterminate	13	3 (23)	10 (77)	
▪ Negative	83	10 (12)	73 (88)	
Vertical margin				0.37
▪ Positive/indeterminate	53	9 (17)	44 (83)	
▪ Negative	43	4 (9)	39 (91)	
Tumor budding				0.69
▪ Yes	39	6 (15)	33 (85)	
▪ No	56	7 (13)	49 (86)	

IQR, interquartile range.

with a score of 1–3 (risk of 18 %), and high risk with a score of > 3 (risk of 50 %; $P < 0.001$) (**Table 2 s**). Among patients with a score of NC-Lymph 0, patients with an NC-Wall score of 0 had a 2 % chance of a lesion in the wall compared with 50 % with an NC-Wall score of 4 ($P = 0.002$) (▶ **Fig. 3**).

Discussion

Our multicenter, multinational Western study on noncurative colorectal ESDs demonstrates that 79 % of the surgical specimens obtained for complementary treatment were free of neoplastic cells in the wall and in the lymph nodes. By studying the risk of residual wall lesions and LNM on this large retrospective cohort, we derived from regression analysis two predictive scores with the aim of better stratifying the risk of residual neoplasia in patients after NC-ESD.



▶ **Fig. 2** Histological examples of the different NC-Lymph scores showing for: **a** score 0, a massive submucosal invasive adenocarcinoma; **b** score 1, an adenocarcinoma with poorly differentiated component; **c** score 2, evidence of lymphatic permeation; **d** score 3, a poorly differentiated adenocarcinoma (left-hand image) and lymphatic invasion (right-hand image).

In the last two decades, ESD has been shown to be a very useful technique for the treatment of colorectal neoplasia, with good outcomes, not only in Eastern countries [16] but also in Western countries [17, 18]. Compared with EMR, ESD offers a higher rate of complete resection and a lower rate of recurrence [18–20], but it is very demanding, with longer procedural times and a greater risk of perforation [19], and a high rate of NC-ESDs is expected. Therefore, we need predictors of the probability of residual wall lesions and of LNM after NC-ESD, in order to decide on the indications for oncological surgery versus endoscopic follow-up.

We analyzed a large multinational case series on NC-ESD with a median endoscopic follow-up time of 1 year for those patients who did not undergo surgery. The majority (96 %) of residual lesions in the scar will be detected in the first 6 months after the resection, and 98 % in the first year according to a large metanalysis [20]. Therefore, the duration of endoscopic follow-up was adequate for detection of residual wall lesions.

In the presence of at least one HRR factor, the ESGE guideline recommends complementary surgery. Our multicenter retrospective case series confirmed lymphatic permeation, VM+/VMx, and poor differentiation, as well as piecemeal resection, to be predictors for a residual lesion among malignant cases. The same was not demonstrated for other factors such as deep submucosal invasion. With regard to the presence of budding, we did not find a statistically significant relationship with the presence of residual disease; however, budding evaluation and scoring may not be homogeneous among the different centers in our study. Therefore, further prospective trials with rigorous evaluation of budding are needed for clarification of this feature as a risk factor for LNM.

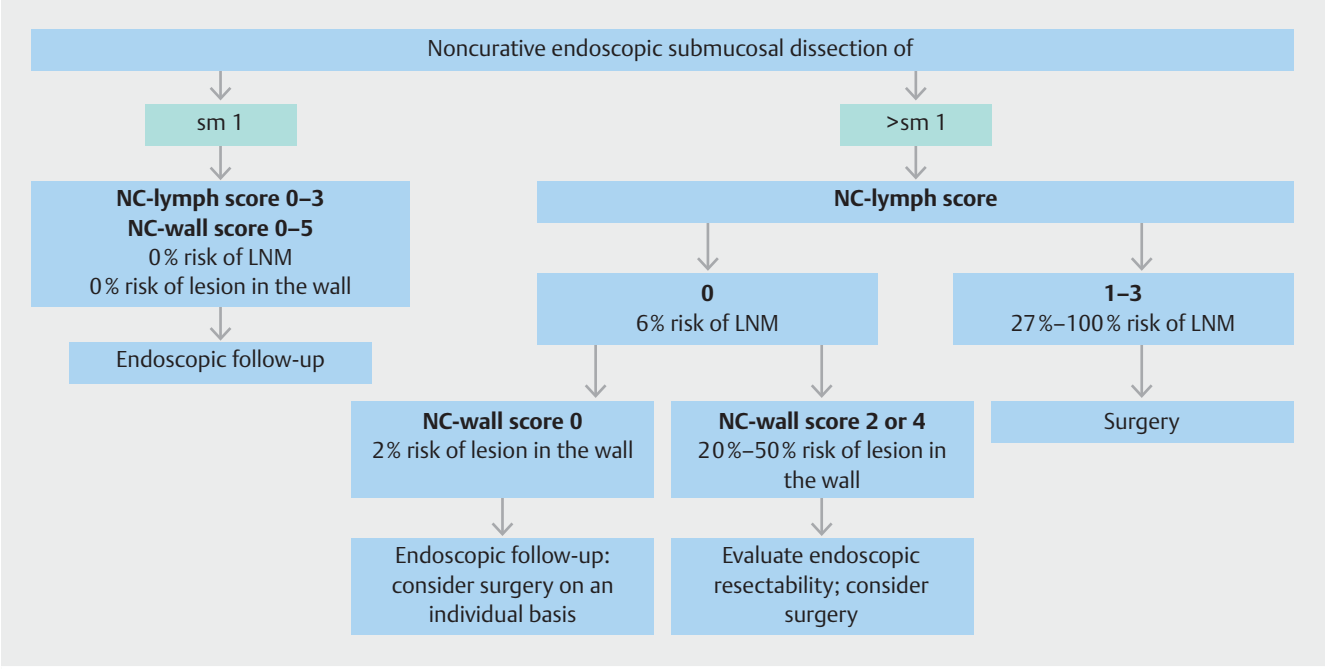
The decision as to whether the patient needs complementary surgery must consider the risk of LNM. In our series, only lymphatic permeation and poor differentiation were independently associated with LNM in the surgical specimen. A smaller series found lymphatic permeation to be the only independent risk factor for the presence of LNM [21]. In fact, this has been reproduced in other studies and it was clearly verified in our cohort [22].

▶ **Table 3** Risk factors for the presence of a residual lesion in the wall (at the endoscopic submucosal dissection [ESD] site) among the 135 patients with a noncurative ESD performed for the treatment of colorectal cancer.

	n	Residual lesion in wall		*P* value
		Yes	No	
Patient characteristics				
Age, mean (SD), years	135	68 (9)	66 (11)	0.54
Sex, n (%)				0.20
▪ Male	84	13 (16)	71 (84)	
▪ Female	51	4 (8)	47 (92)	
Lesion characteristics				
Lesion size, median (IQR), mm	135	42 (29–60)	40 (25–60)	0.77
Paris classification				0.56
▪ Is	31	6 (19)	25 (81)	
▪ IIa	30	4 (13)	26 (87)	
▪ IIa + Is	40	3 (8)	37 (82)	
▪ Any IIc component	29	3 (10)	26 (90)	
▪ Other	5	1 (20)	4 (80)	
Location				0.12
▪ Colon	60	11 (18)	49 (82)	
▪ Rectum	75	6 (8)	69 (92)	
Laterally spreading tumor (LST) morphology				0.60
▪ Granular homogeneous	13	1 (8)	12 (92)	
▪ Granular nodular mixed-type	53	5 (9)	48 (91)	
▪ Nongranular flat-elevated	12	3 (25)	9 (75)	
▪ Nongranular pseudodepressed	18	2 (11)	16 (89)	
▪ Non-LST morphology	39	6 (15)	33 (75)	
Procedure characteristics				
ESD duration, median (IQR), minutes	105	110 (60–191)	100 (60–165)	0.88
Complementary techniques				0.05
▪ Knife-assisted resection/hybrid	28	7 (25)	21 (75)	
▪ Traction clip-line	2	1 (50)	1 (50)	
▪ Pocket	10	0	10 (100)	
▪ Underwater	2	0	2 (100)	
▪ None	93	9 (10)	85 (90)	
Resection type				**< 0.001**
▪ En bloc	123	11 (9)	112 (91)	
▪ Piecemeal	12	6 (50)	6 (50)	
Histopathological analysis				
ESD staging				0.12
▪ sm1	15	0	15 (100)	
▪ > sm1	120	17 (14)	103 (86)	
Differentiation				**0.03**
▪ Well/moderate	118	12 (10)	106 (90)	
▪ Poor	17	5 (29)	12 (71)	
Lymphatic permeation				0.450
▪ Present	17	3 (18)	14 (82)	
▪ Absent	118	14 (12)	104 (88)	
Venous permeation				> 0.99
▪ Present	13	1 (8)	12 (92)	
▪ Absent	99	9 (14)	85 (86)	
Horizontal margin				0.19
▪ Positive/indeterminate	24	5 (21)	19 (79)	
▪ Negative	111	12 (11)	99 (89)	
Vertical margin				**0.002**
▪ Positive/indeterminate	71	15 (21)	56 (79)	
▪ Negative	64	2 (3)	62 (97)	
Tumor Budding				0.69
▪ Yes	51	7 (14)	44 (86)	
▪ No	79	9 (11)	70 (89)	

IQR, interquartile range.

For LNM, little is known about the individual relevance of the other high risk factors in HRRs. Some studies have not shown deep invasion to be an independent risk factor on multivariate analysis [23], others found 2000 µm to be the cutoff for a higher risk of LNM [24]. A meta-analysis on retrospective studies showed that 2-mm deep submucosal invasion, as compared with 1-mm deep, was related to a higher risk of LNM [25]. A large Japanese study on surgical specimens showed that none of the T1 cancers with submucosal invasion < 1000 µm presented with LNM [26]. In our cohort, we also did not find any sm1 T1 cancers with LNM, regardless of the presence of other risk factors. Similarly, the presence of deeper invasion as a risk factor



▶ **Fig. 3** Management of the patients according to the predictive scores.

for LNM did not find statistical significance in our cohort. In fact, >sm1 T1 cancers without any other risk factors (i. e. negative for lymphovascular permeation, budding, VM+/VMx, piecemeal resection) had a 0% chance of LNM or a lesion in the wall. Three patients were identified with metastasis during follow-up in our cohort, but late metastatic disease after an NC-ESD was not a primary end point in this study and it should be evaluated in prospective trials with long-term follow-up.

Surgery after an NC-ESD in the colorectum is usually effective and safe [27, 28]; however, colorectal surgery can lead to morbidity and a decreased quality of life, so the criteria for referral to surgery must be refined. We suggest that an NC-Lymph score >0 warrants surgery, owing to the high risk of LNM (above 27%). For patients with an NC-Lymph score of 0, a rigorous assessment of deep invasion, vertical margin, and budding characterization should be performed, and the decision must be individualized. Among patients with malignant lesions that did not directly qualify for surgery (NC-Lymph score 0), patients with an NC-Wall score >0 should undergo close endoscopic follow-up or surgery, and those with a score of 0 could probably be followed-up by endoscopy, because of the low risk of a colorectal lesion at the scar.

The application of computer-aided models for predicting LNM might become a potential option to help with validation of our two scores in big data [29]. A recent study reported that artificial intelligence significantly reduced unnecessary additional surgery after endoscopic resection of colorectal T1 cancer in comparison with the current guidelines [30].

Our study has strengths and limitations. The main strength is that it is a multinational large series on NC-ESDs, with the participation of multiple referral endoscopists and institutions, which allowed us to have a significant number of cases with and without a residual lesion in the Western setting. We were able to establish a tool to identify those patients who will benefit from surgery and those who would have a high probability of being submitted to a futile intervention.

The main limitations relate to the observational nature of the study and the heterogeneity of the ESD technique, which reflects daily clinical practice. In addition, follow-up losses and the absence of complementary surgery owing to refusal or comorbidities may represent a selection bias. Another limitation is that, despite gathering data from several centers, the rate of NC-ESD among the total number of ESDs is low; because of this, the predictive scores were calculated using the entire cohort, which did not allow us to split the sample in order to have external validation. We used the resampling methodology to mitigate this issue, but subsequent clinical trials should be performed for external validation and to eventually refine these scores in order to incorporate them into clinical algorithms.

In conclusion, with this large multicenter retrospective Western case series of colorectal NC-ESD, we found that none of the patients with an NC-ESD of an sm1 T1 colorectal cancer had a residual lesion in the wall or in the lymph nodes, even with the presence of other high risk criteria. Similarly, >sm1 T1 cancers without any other risk factors did not present residual lesions during the follow-up. Among >sm1 T1 cancer patients, lymphatic permeation and poor differentiation in the ESD specimen were the only independent factors for LNM, and its presence should warrant surgery. Lesions removed by piecemeal resection that are poorly differentiated and without free vertical margins have the highest risk of a residual lesion in the wall. The developed scores could be helpful to reduce the rate of unnecessary adjuvant surgery following colorectal NC-ESD.

Competing interests

The authors declare that they have no conflict of interest.

Clinical trial

Trial Registration: ClinicalTrials.gov | Registration number (trial ID): NCT04484311 | Type of study: Retrospective multicenter Study

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